REMARKS

Entry of the amendment and reconsideration of the rejection of the claims in view of the following Remarks is respectfully requested.

Claim 1 has been amended. Support for the amendment can be found at page 6, lines 6-12, and in original claim 2. Claim 10 has been amended to provide proper antecedent basis.

Claims 2-7, 9, 11-13, and 20 have been cancelled without prejudice or disclaimer. Claims 3, 5-7, 9, 11-13, and 20 were previously withdrawn as being drawn to a non-elected invention. Applicants reserve the right to pursue prosecution of these claims in one or more continuation applications.

Therefore, claims 1, 8, 10, 14-15, 18-19, and 21 are pending in the application.

Withdrawn Rejections/Objections

Applicants acknowledge the withdrawal of the rejection to the specification regarding the use of trademarks.

Applicants acknowledge the withdrawal of the rejection of claims 1, 2, 8, 10, and 14 under 35 U.S.C. 102(b) as anticipated by Martin et al.

Applicants acknowledge the withdrawal of the rejection of claims 1, 2, 4, 8, 10, 14-15, and 18 under 35 U.S.C. 102(a) and 102(e) as anticipated by Keyt et al.

Applicants acknowledge the withdrawal of the rejection of claims 1, 2, 4, 8, 10, 14-15, and 18-19 under 35 U.S.C. 103(a) as unpatentable over Keyt et al.

35 U.S.C. 112, second paragraph

Claim 10 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Examiner contends there is insufficient antecedent basis for the phrase "effective amount of VEGF." Claim 10 as amended recites a "VEGF variant." Applicants submit that there is sufficient antecedent basis for this phrase. Withdrawal of the rejection is requested.

Enablement

Claims 1, 8, and 10 were rejected under 35 U.S.C., first paragraph for alleged lack of enablement. The Examiner contends that the specification does not enable methods of treating any nitric oxide associated disorder using VEGF variant or VEGF receptor agonist. Applicants traverse this rejection.

While not acquiescing to the rejection and solely to expedite prosecution, claim 1 now recites a method of treating a nitric oxide associated disorder, wherein the disorder is hypertension, diabetes, thrombosis, angina, atherosclerosis, or heart failure. The Examiner has acknowledged that the specification provides enablement for the treatment of these disorders. Withdrawal of this rejection is therefore requested.

Claims 1-2, 8, 10, 14, 15, and 21 are rejected for alleged lack of enablement. The Examiner contends that the specification does not reasonably enable any VEGF variant or VEGF receptor agonist that selectively binds KDR receptor. Applicants traverse this rejection.

"For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient [to enable the claims] if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." MPEP 2164.02. Only a reasonable correlation between enablement and the scope of the claims is required.

The rejected claims recite methods for treating nitric oxide (NO) associated disorders, or methods of stimulating sustained production of endogenous NO in an endothelial cell, using VEGF variant or VEGF receptor agonists that are selective for the KDR receptor. Applicants submit that the claims are fully enabled, because their scope reasonably correlates with the enablement provided by the disclosure.

Applicants have provided working examples for a method of producing VEGF variants, and selecting for variants displaying selectivity for the KDR receptor (Examples 6 and 7). Using this method, Applicants obtained and disclosed twenty-nine different variants having KDR selectivity (Table 2). The specification further discloses in Table 2 the precise nature of the differences in amino acid sequence between native VEGF and the variants. Table 3 discloses the selectivity and properties of the variants. With respect to Table 3, Applicants note that the second number in each column indicates the fold difference in binding affinity of the variant relative to the control. For example, variant LK-VRB-1s has the same binding affinity for the KDR receptor as the control, while its binding affinity to FLT-1 receptor is 6000-fold less than the VEGF control. Applicants submit, therefore, that the specification provides representative examples of the claimed genus such that the genus is fully enabled.

The Examiner contends, however, that the claims are not enabled because Applicants have not disclosed which residues outside of the KDR receptor binding region or FLT-1 receptor binding region can be mutated to produce VEGF variants or VEGF receptor agonists selective for the KDR receptor. Applicants disagree. Applicants have disclosed which regions of VEGF are important for binding to KDR receptor and FLT-1 receptor (page 4, lines 1-22 and Example 6). Furthermore, and as stated above, Applicants have disclosed 29 different variants having KDR selectivity. Therefore, Applicants have provided extensive guidance to one of skill in the art concerning the nature of mutations that could be made to obtain a VEGF variant selective for the KDR receptor.

Applicants submit, therefore, that it would not require undue experimentation to obtain other variants within the claimed genus of variants selective for the KDR receptor. Applicants submit that methods of screening variants for selectivity to a receptor are routine in the art. Even an "extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *MPEP 2164.05(b)* (citing *In re Colianni*, 561 F.2d 220, 224 (CCPA 1977).

As discussed above, Applicants have provided extensive amounts of guidance with respect to the VEGF variants or VEGF receptor agonists. Applicants have disclosed extensive

functional information concerning which regions of VEGF are important for KDR and FLT-1 binding, and have provided a large number of representative species within the claimed genus of variants selective for the KDR receptor. Therefore, Applicants respectfully submit that there is no reason of record as to why one of skill in the art could not expect to make and use the full genus of Applicants' invention as claimed without undue experimentation, in view of the extensive guidance given by the specification. For the foregoing reasons, withdrawal of this rejection is respectfully requested.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: Sept. 20, 2004

Katherine M. Kowalchyk
Reg. No. 36,848

23552
PATENT TRADEMARK OFFICE